DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
M3190n
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October 29, 1999

VIA FEDERAL EXPRESS

Dr. Ricardo B. Levy
President & Chief Executive Officer
Catalytica, Inc.
430 Ferguson Drive
Mountain View, CA 94043

WARNING LETTER
(00 ATL-09)

Dear Dr. Levy:

During an inspection of your manufacturing facility covering your manufacture of Active Pharmaceutical Ingredients (APIs) and tablet products located in Greenville, North Carolina conducted on June 28, 1999 through July 1, 1999, our investigators documented significant deviations from Current Good Manufacturing Practices (CGMPs) in the manufacture of APIs.

These deviations cause the APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (Act). Section 501(a)(2)(B) of the Act requires that drugs are manufactured, processed, packed, and held in accordance with CGMPs. No distinction is made between APIs and finished pharmaceuticals, and failure of either to comply with CGMPs constitutes a failure to comply with the requirements of the Act.

We have reviewed your July 26, 1999, August 11, 1999, August 23, 1999, October 11, 1999, and October 20, 1999 correspondences. We note that many of the deficiencies are in the process of being corrected.

At the time of your inspection, your firm had failed to complete process validation for the 17 Active Pharmaceutical Ingredient (API) products currently manufactured. Of the 69 modules that have manufactured finished product and/or intermediates, only 33% have completed prospective process validation. Of those 23 that are complete, 10 are the finishing steps (milling, drying, etc.) conducted in Building 34. This indicates that only 13 of the modules addressing the critical process steps other than finishing/milling/drying have completed process validation.

Your firm was informed during the 8/94 inspection of FDA's expectations in the area of API validation. Plans were put in place 12/1/94 to validate the processes in the Chemical Manufacturing Operations (CMO). We recognize that the validation effort was complicated by the corporate change since 1994, namely the merger with [redacted] and the ensuing sale of the company to Catalytica, Inc. However, the CMO production summary indicates that since 1/98 CMO routinely manufactured most of the major products scheduled for validation.

Our investigators spoke with selected members of management and the CMO validation staff about the number of projects scheduled versus the number of employees in that department. The Department currently has seven employees including the Section Head, and of the seven, three have been recently hired. This department is responsible for all process, cleaning, equipment validation, validation change controls, and all the corresponding reports, data, and protocols. This seems like an inadequate number of trained employees. While you identified 110 open validation projects during the inspection, at the meeting on August 6, 1999, you corrected that number to 85 open validation projects. We feel that the lack of adequate staff to perform validations has likely contributed to the slow progression of validation activities over the past few years. Meanwhile, your firm is actively seeking and bringing on new products and processes.

We acknowledge that your most current response, dated October 20, 1999 indicates that you have completed process validation of 36 of the 69 manufacturing modules for fifteen products. While you have provided a timetable for the completion of the process validation for the majority of your products manufactured during 1999, you have failed to provide a timetable for the completion of the process validation of all of the products you manufacture. We recognize that you utilize a "Batch by Batch release procedure, which appears to be concurrent validation, for at least three low volume APIs, however, you have not provided a timetable for completion of validation for these products.

During the inspection, the investigators noted that Catalytica, Inc. had no procedures for quarantining new products that have not completed prospective validation. The example cited by the investigators concerned 31 batches of [redacted] API (new product) having been released and shipped beginning in 8/98. However, the validation report referencing validation activities performed in 11/98 had not been finalized and/or approved to date.

Your July 26, 1999 response committed to implementing procedures to prevent the release of any new API intended for commercial use until completion of validation. You also committed to prevent the release of any existing API for which a change in the manufacturing process has been assessed to impact validation. This response included four Standard Operating Procedures (SOPs), two of which were in draft status. We question why these procedures have not been finalized. In addition, you have not committed to prevent the release of all existing APIs until the completion of validation.

Also, your firm manufactures [redacted] API for use in GS parental [redacted] tablets [redacted], [redacted] USP Ointment and Suspension [redacted] and [redacted]. The [redacted] used in these products has different specifications for items such as chromatographic impurities and particle size. Our inspection noted that your firm rejected 24 of 41 batches (59%) of [redacted] produced in 1998 and 10 of 17 batches (59%) manufactured in 1999. Your firm's process for manufacturing [redacted] for use in the [redacted] process is not capable of consistently meeting specifications and therefore is not validated.

Your July 26, 1999 response committed to not manufacturing the [redacted] for use in the [redacted] process, and purchasing this API from an outside vendor. While this is an acceptable correction, we do not agree with your assertion in your response that the [redacted] is a starting material and not an intermediate in the synthesis of [redacted] We consider [redacted] Chemical Grade a finished API, whose process should be validated prior to using this API in the synthesis of another API.

Our inspection revealed that your cleaning validation for API products has not been completed for the chemical process/synthesis trains (chemical residue and detergent removal) and dryer blender/finishing trains (detergent removal). We consider this a serious deviation in that your equipment is not dedicated (except the [redacted] manufacturing process), and your firm manufactures several antineoplastic APIs. Again, we feel that your firm has progressed slowly in the completion of this project. We acknowledge that the target dates for completion of the cleaning validation were proposed during the August 6, 1999 meeting, which indicate that completion is not scheduled until December 2000. While you also committed to performing chemical residue testing until the validation was completed, this time period for completion seems inappropriately long. What rational was utilized for determining this completion date? It appears that your schedule for cleaning validation completion was based on completion of the building involved in the process. Did your rational for this approach consider the high volume products or the most toxic products to minimize the impact of possible contamination?

The inspection noted that review of process validation summaries lacked assay specifications for in-process blend uniformity samples. The firm's acceptance criterion is a relative standard deviation (RSD) not exceeding 6.0% for each active ingredient, but there is no assay criterion such as 90-110%. A relative standard deviation could be met although some or all samples were outside a 90-110% assay range; this, in turn, would be objectionable without further testing or investigation.

While your July response states that you have incorporated both acceptance criteria and the RSD for all new process qualifications, you have failed to address review of your previous process validations summaries to ensure that previous assays were not out of specification.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that all drugs be manufactured, processed, packed, and held according to current good manufacturing practices. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Until the Agency reinspects your API facilities and confirms that these deficiencies have been corrected, this office will recommend disapproval of all New Drug Applications, Abbreviated New Drug Applications, and export certificates.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in further regulatory action without further notice. Possible actions include seizure and/or injunction.

You should notify this office in writing by November 22, 1999 of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your reply should be addressed to Barbara A. Wood, Director of Compliance, at the address noted in the letterhead.

Sincerely,

Ballard H. Graham, Director
Atlanta District